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# Commentary: A review on BPA-MDM2-Breast cancer Loop

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MDM2, Murine Double Minute 2

WHO, World health organisation

## Introduction:

The last six decades have witnessed the massive introduction of various bioactive synthetic chemicals. At the same time, epidemiological studies revealed the increased prevalence of many metabolic disorders. One of the compounds introduced was Bisphenol A (BPA). BPA is a synthetic phenol and was first reported by a Russian chemist Aleksandr Dianin in 1891 and synthesized via the condensation of acetone with phenol by Zincke in 1905 [1]. BPA is a plasticizer extensively used in various industries to soften and shape plastic materials [2]. It is present in various daily use plastics such as polycarbonate plastics, epoxy resins, food containers, packaging polythene papers, dental sealants, flame retardants, baby bottles, water bottles, store and ATM thermal receipts, plastic packaged foods, animal cages, sports, medical and dental filling equipments, household electronics, children's toys and even the eyeglasses. BPA easily leaches out from the food containers and was detected in considerable amount in human blood and urine samples. Human exposures have been reported due to other minor sources such as mouthing of toys, cigarette filters, household detergents and personal care products. So, BPA is ubiquitous in modern world and avoidance of exposure is impossible [3]. In 1953, global production of BPA was used for the manufacture of polycarbonate polymers and epoxy resins. In 2011, BPA production was 5.5 million metric tons per year globally. In 2015, the global production of BPA increased to 7 million metric tons per year. In 2017, US alone contribute the highest volume of 5 million metric tons per year with increasing demands of 13% in Asia and 19% in India [1]. As an endocrine disruptor, BPA acts via the estrogen and androgen receptors resulting in various cancers like lung cancer( through inhalation of BPA in the polluted atmosphere), breast cancer, cervical cancer, reproductive capacity impairments like miscarriages, thyroid disorders, neurodegenerative and neurodevelopmental disorders(Alzheimer's disease, Rett syndrome, Parkinson's disease), neurobehavioral problems such as attention deficit hyperactivity disorder(ADHD), altered growth, early secondary sexual maturation, early puberty, Obesity promotion(Type II DM) and other modern metabolic disorders [4, 5]. BPA also down regulates p53 expression and also mutates tumor suppressor gene p53 [6]. MDM2 (HDM2) and MDMX (homolog of MDM2) execute their oncogenic activity mainly by negatively regulating the stability and activity of the p53 protein. Of these, MDM2 inhibits both the stability and activity of p53. BPA acts via the estrogen receptor and causes overexpression of MDM2 gene which down regulates p53 expression and leads to tumorigenesis [7]. Therapeutic approaches have been made by targeting the p53-MDM2-MDMX loop in the past decades [8]. Developed countries like USA, Canada, European Union, Argentina, Brazil, Ecuador and Turkey have banned the use of BPA especially in daily use plastics used by infants and children and food contact plastics. But developing countries like India, Japan, Indonesia, Nigeria, Bangladesh, Pakistan, etc. Currently do not have any restrictions on the use of Bisphenol A in the manufacture of food contact plastics [9, 10]. According to WHO, Cancer is one of the leading cause of death worldwide.

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Presently, Breast cancer is the major type of cancer among Indian females with low survival rate of 66%. Many modifiable risk factors like use of alcohol were preventable. But the exposure of environmental carcinogen such as endocrine disruptors like Bisphenol A is not regulated in India which may be the cause of increased incidence of hormone related cancers like breast cancer and other metabolic disorders. In 2010, World Health Organization (WHO) and Food and Agricultural Organization (FAO) issued a safe Tolerable Daily Intake of BPA to be 1.5-4.2µg/kg body weight/day. In 2015, European food safety authority revealed the reference Tolerable Daily Intake (TDI) of BPA from 50µg/kg body weight/day to 4µg/kg body weight/day [1].

**Biohazards of BPA:**

Hammad AY et al. conducted an analysis of BPA by UV Visible Spectrophotometry in seven samples such as good and bad stored drinking waters, normal saline infusion, nasal and eye drops, injectable forms of ear drops and distilled water collected randomly from Khartoum state of Sudan. They observed a considerable amount of BPA leached into the samples under normal conditions. This finding poses a significant human health risk of BPA exposure from medically related drug samples [11, 12]. Corrales J et al. reported that the occurrence of BPA in natural environment such as surface water, effluents, bio solids, sewage sludge, sediments, soil and air causes bioaccumulation in wildlife and humans globally across Asia, Europe, North America. They found that the maximum concentration of BPA was observed in urban ecosystems of Asia than in Europe [13]. A study conducted by Liu J et al. observed that BPA had been found in the liver, gills and muscles of fishes in Dianchi Lake, China. Bioaccumulation of BPA was found highest in the liver hepatic cells where most metabolism, biotransformation and excretion of contaminants take place. Next to the liver, the maximum bioaccumulation was found in the gills which are in direct contact with the water, where the passive exchange of contaminants between the environmental water and epithelium of bronchial gills takes place [14]. Similarly, in Netherlands the BPA concentration levels were detected in fish muscle samples by Belfroid A et al. [15]. And also in UK, the BPA concentration in liver tissues of fishes had been reported by Lye CM et al. [16].

**Human exposure to BPA:**

Bisphenol A (BPA), with properties similar to diethylstilbestrol (a synthetic form of estrogen) binds with steroid receptors and exerts endocrine disrupting effects including hormone dependent tumors such as breast cancer and metabolic disorders like polycystic ovary syndrome which is reported by Konieczna A et al. [17]. Estrogen receptor alpha (ERα) plays an important role in the onset and progression of breast cancer. BPA binds with both ERα and ERβ and causes breast cancer [18]. There are several studies-international and national shows that BPA on exposure to heat, acidic or basic pH levels easily leaches out from food containers and was detected in human blood and urine samples. And some adverse effects have been observed in experimental animals when exposed to low doses of BPA such as increased prevalence of prostate and breast cancer, early puberty, low semen and urogenital abnormalities in male etc. [19]. Human BPA exposure through consumption of canned foods has been estimated to be 6.6mg/person/day which then enters blood stream. In human urine samples, with detection limit of 0.4µg/liter of urine, BPA were detected in 92.6% of the samples examined [1]. When exposed to BPA coated thermal receipts, an average dose of 71µg/day enters through the skin of check-out clerks and cashiers and it is ten times more when the fingers were wet and greasy. When the use hand sanitizers, the transdermal penetration increases upto 100 fold [1]. The worst case scenario is that a meta-analysis concluded that 0.013 to 30mg of BPA may be released within 24 hours of implantation of dental fillings [13]. Having a half-life of 5.30 hours, BPA is eliminated primarily through glucuronidation [20].

In a study involving the estimation of plasma levels of BPA in fertile and infertile women, BPA was detected in 75.6% of infertile women [21]. A study revealed that 81% of 315 urine samples collected in USA and Asia (India, China, Japan, Korea, Kuwait, Malaysia and Vietnam) contains BPA and its levels were found at a higher concentration in urine samples as it is primarily eliminated through urine via glucuronidation than blood samples [22]. Another study published in 2018 in International Journal of Research in medical Sciences involving 150 patients of young males and females from areas of northern India surrounding Varanasi had various metabolic and reproductive disorders. All patients had detectable levels of BPA in their Urine samples [23]. Cuomo D et al. reported that through ingestion, transdermal penetration and inhalation BPA enters into the human body and it has been found that 90% of the tested human's biological fluids such as

amniotic fluid, neonatal blood, placenta, cord blood and human breast milk contain BPA with highest levels being observed in infants and children which may leads to pathogenesis in old ages [24]. A study conducted in Korea reported that there is an association between the presence of BPA and risk of breast cancer in Korean women. It also reported that there is no significant differences in the BPA exposure levels between the cases and controls when their samples are examined [25]. Wazir U and Mokbel K considered that there is an urgency to use a safer alternative to BPA such as Syringaresinol to avoid various pathologies caused by BPA such as oncogenesis and various metabolic disorders. They also reported that BPA exposure in key points of human developmental stages such as during pregnancy and puberty is believed to increases the risk of various pathologic conditions like breast cancer in Later stages of life [26].

On exposure, BPA enters blood and interacts with human serum albumin, heme moiety of hemoglobin and cytochrome c and causes structural and conformational changes [27, 28]. A study reported that the UV visible absorption spectrum of human blood had increased absorbance and maximum peak wavelength at 250-300nm and 360-450nm. BPAQ (the active metabolite of BPA) binds with hemoglobin (Hb), human serum albumin (HSA), cytochrome c and shifts (blue shift) the maximum wavelength peak from 283nm to 274nm and 411nm to 408nm due to structural changes in Hb, Cyt C and HAS-BPAQ complexes [27]. The maximum wavelength peak of 280nm is due to the formation of HAS-BPAQ complex [28]. BPA is converted into BPAQ in vivo and it adducts with the nucleotides which may leads to DNA damage, mutagenicity and carcinogenicity. The in vivo BPAQ adduction with nucleotides had been demonstrated by Edmunds SJ et al. [29].

**MDM2 gene and Oncogenesis:**

Bond GL et al. reported that a single nucleotide polymorphism in MDM2 gene (T to G change) down regulates p53 and results in carcinogenesis. The MDM2 SNP 309 mutation site is present in the first intron of the intronic promoter region. A wild type allele SNP 309 (T/T) in MDM2 promoter region have decreased affinity to Sp1 DNA binding site and does not cause the degradation of p53. Whereas the homozygous type SNP 309 (G/G) in the MDM2 promoter region have more binding affinity to Sp1 transcription factor and results in overexpression of MDM2 which leads to the degradation of p53 response. This results in decreased apoptosis and increased tumorigeneis. The presence of SNP 309 T to G change extended the length of Sp1 DNA binding site for transcription and increased MDM2 expression which results in heightened MDM2 mRNA which causes degradation or reduced expression of p53 tumor suppressor gene. This also leads to the inability to properly stabilize p53 in response to cellular stresses. They also reported that when treated with the inhibitors of Sp1 transcription factor like etoposide and mithramycin A, increased cell death was observed in MDM2 homozygous type allele (SNP 309 G/G) while it was not seen in wild type allele(SNP 309 T/T) [30, 31]. Ebid GT et al. reported that the single nucleotide polymorphism in p53-MDM2 (a T to G)/ p21 pathways may lead to variety of tumors such as lung, esophageal, colorectal, breast and gastric cancer. They also observed that a combined allele frequency of TG and GG in 69% of population taken which shows the increased risk of Acute Myeloid leukemia [32]. Gryshchenko I et al. reported that MDM2 overexpression due to SNP 309 G/G showed increased risk factor for chronic lymphocytic leukemia [33]. Onat et al. concluded that increased MDM2 SNP 309 G allele frequency has increased risk for developing Bladder cancer ($p < 0.01$) [34]. Xiao M et al. studied the association of MDM2 and risk of nasopharyngeal carcinoma and concluded that MDM2 SNP 309 GG homozygous type posed an increased expression of MDM2 gene and increased MDM2 mRNA level was found in nasopharyngeal carcinoma tissues. This shows that MDM2 SNP 309 GG increases the risk of nasopharyngeal carcinoma [35]. Another study conducted by Akkiz H et al. in 110 hepatocellular carcinoma patients and 110 cancer free controls found that there is a significant association between MDM2 SNP 309 and risk of hepatocellular carcinoma. They observed an increased frequency of G allele in patients than the controls [36]. Hong Y et al. reported that there is an increased risk of esophageal squamous cell carcinoma associated with MDM2 SNP 309 GG homozygous type [37]. Avirmed S et al. reported that in a study population involving 79 healthy controls and 63 bladder cancer patients, the MDM2 SNP 309 GG homozygous genotype was associated with increased risk of carcinoma of urinary bladder. They also reported that MDM2 SNP 309 TG heterozygous genotype is also associated with the risk of bladder cancer involving other factors such as urinary tract diseases, alcohol use excluding smoking habit [38].

A meta-analysis of 66 case-control studies conducted by Wan Y et al. concluded that MDM2

SNP 309 homozygous GG genotype and TG heterozygous genotype were associated with the risk of tumorigenesis in Asian and European populations. They also reported that particularly G variant showed elevated risk of breast cancer [39]. Gao C et al. reported that MDM2 increases tumor cells migration in triple negative breast cancer and also increases proliferation of breast epithelial cells in an $ER\alpha^{+}$ dependent manner [40]. Meidl H et al. reported that in a study population of 406 breast cancer patients and 254 controls, MDM2 SNP 309 TT is associated with increased p53 degradation. In their study population the wild type MDM2 SNP 309 TT genotype was associated with the risk of onset of breast cancer at a younger age. They also reported that MDM2 SNP 309 GG homozygous genotype was associated with risk of onset of breast cancer at older age. They concluded that MDM2 SNP 309 TT wild type genotype was associated with increased Tp53 mutation and earlier onset of the risk of breast cancer [41]. Boersma BJ et al. investigated a case-control study of 293 breast cancer patients and 317 normal control subjects and reported that the variant MDM2 SNP 309 GG homozygous genotype causes degradation of p53 protein than the wild MDM2 SNP 309 TT genotype [42].

Tsuiki H et al. reported that there is no association between homozygous types G/G of MDM2 SNP 309 with p53 mutation status. They concluded that MDM2 causes cancer in a way independent of p53 pathway [43]. In a study involved of 726 lung cancer patients conducted by Enokida Y et al. demonstrated that there is no association between the MDM2 SNP 309 T>G and the risk of lung cancer [44]. Millikan RC et al. also reported that there are no significant differences between the breast cacner cases and controls in MDM2 SNP 309 polymorphism [45]. Singh V et al. reported that there were no significant associations between MDM2 and p53 mutations with heritable breast cancer risk among Indian women. They concluded that MDM2 SNP 309 polymorphism alone is not significantly associated with the risk of breast cancer [46]. A study conducted in 549 familial breast cancer patients by Wilkening S et al. reported that MDM2 SNP 309 does not influence the risk of breast cancer. But there is an overall 16% of breast cancer patients carried GG homozygous type. They concluded that MDM2 overexpression cause DNA damage without the interaction with p53 in a p53 independent manner. And also they observed that 549 breast cancer patients do not carried BRCA1/2 mutations [47]. Vivenza et al. reported that MDM2 SNP 309 is an important biomarker for treating cancer patients with cis-platin based cancer radiotherapy [48]. Tu HF et al. also demonstrated that MDM2 SNP 309 mutation status as a confirmatory test after cancer radiotherapy [49]. Shivam V et al. reported the association of MDM2 SNP 309 G variant with breast cancer risk [58]. This indicates that MDM2 SNP 309 (a T to G change) increases the risk of tumorigenesis. Thus MDM2 SNP 309 helps in validating the therapeutic efficacy and prognostic prediction.

**BPA-MDM2-Oncogenesis loop:**

Bilancio A et al. reported in a study that even 1nm BPA induces cell proliferation in human prostate cancer cells LNCaP via androgen receptor (AR). BPA increases prostate cancer progression by inducing hormone resistant either through receptor antagonism or cell cycle arrest of hormone dependent cells. Growth inhibition in androgen dependent prostate cancer cell lines (LNCaP and LAPC4) is reported due to the treatment of high doses of BPA (eg. 10µM) [50]. BPA induces cell proliferation in human breast cancer cells via both ERα membrane associated receptors and non-genomic pathways by converting cells from $G_0$-$G_1$ to S-phase. It also acts through G protein coupled estrogen receptors (GPR30) in both ER positive and ER negative breast cancer cells. The signaling pathways reported were PERK1/2 and MAPK P44/42 [50, 51]. Low doses of BPA and physiological estrogen concentration stimulates cell proliferation in MCF-7 CV breast cancer cells and also alters the E-cadherins and N- cadherins [52]. Isomers of MDM2 were overexpressed in three breast cancer cell lines such as MCF7, T47D and MDA-MB231 [53]. ERα also overexpressed in MCF-7 breast cancer cell lines [54]. The negative regulation of p53 tumor suppressor gene by overexpression of ERα and MDM2 SNP 309 G allele was reported in MCF 7 breast cancer cell lines [55]. Both the overexpression of ERα and MDM2 suggests that there is a direct regulation of estrogen receptors by MDM2 gene. V Shivam et al. reported that there is a correlation associated between presence of bisphenol-A and MDM2 gene mutation and increases the risk of breast cancer [58].

In summary, bisphenol-A and its active metabolites play an important role in the pathogenesis of various metabolic disorders in humans. Thus reduction in the daily exposure of environmental BPA may provide a beneficial effect in reducing the incidence of modern metabolic disorders. Further, the possible role of bisphenol-A and its active metabolites

in the risk of metabolic disorders and oncogenesis should be further assessed with large sample size.

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